COMPUTATIONAL MECHANOBIOLOGY: MAY THE FORCE BE WITH YOU

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Mechanics regulates cell behaviour

Mechanical forces are important regulators of physiological and pathophysiological processes. It has long been recognized that e.g. during embryonic development cell-cell and cell-matrix-mechanical interactions are crucial for understanding morphogenesis. In a way, this does not come as a surprise, as morphogenesis – literally the 'creation of shape' – involves the motion of cell and tissue constituents, which must obey the laws of classical mechanics. The effect of mechanics on cell and tissue physiology goes much further than their passive deformation:

- First, cells are able to contract, meaning that they shape their own extracellular environment by actively deforming it, a phenomenon which was already observed in 1980 by Harris and co-workers, by culturing various cells on deformable silicone substrates (Harris et al., 1980).
- Second, a cell has a molecular mechanical network that comprises adhesion molecules that enable the cell to adhere to the extracellular matrix (such as integrins) as well as to neighbouring cells (such as cadherins), molecules that constitute the cytoskeleton (such as actin) and a wide range of 'linker' molecules that connect adhesion molecules to the cytoskeleton, the cytoskeleton to the nucleus and cytoskeletal filaments to each other. In this way, forces can be transduced from the extracellular space to the intracellular space, down to the cell's DNA (Wang et al., 2009).
- Third, cells are able to convert mechanical into chemical energy (mechanotransduction, mechano-chemical conversion), which is believed to rely on mechanics-induced conformational changes of molecules, in this way changing their activity (Ingber, 2006).

These three aspects are intimately related, meaning among others that cell contractility affects force transduction and mechano-chemical conversion on the one hand, and that mechano-chemical conversion can lead to changes in the cell's contractile and molecular mechanical properties on the other hand. In addition, many of the reactions that are part of a signaling cascade seem to take place in a solid state, meaning that the reactants are not freely 'floating' in the cytosol, but instead are bound to e.g. cell adhesion sites (so called focal adhesion complexes) or the cytoskeleton, which could act as a scaffold for the chemical reactions. Given the fact that these are also the primary sites for force transduction, mechanics could modulate the kinetics and/or equilibrium of these reactions, thereby providing direct feedback from mechanics to chemistry. Finally, many chemical receptors (such as growth factor receptors) have a number of downstream targets that control cytoskeletal organization and mechanics (i.e. feedback from chemistry to mechanics). In summary, it means that mechano-chemical feedback is a fundamental mechanism that affects cell behaviour in every aspect, such as shape, migration, division, differentiation and death.

How to deal with mechanics in a computational biology context?

Given its importance and omnipresence, one must consider to include mechanical aspects in computational biology and physiology, especially if computational models are intended to study cell and tissue organization and function. This idea is clearly not new, as models that deal with tissue

organization and that rely on cell-matrix mechanical interactions have been pioneered by Oster, Murray and co-workers in the eighties (see Murray (2003) for an overview). Murray also highlights a number of reasons why we should care about mechanics when dealing with biological and physiological problems such as tissue organization:

- Mechanical signals act as additional feedback signals to increase the stability (robustness) of a biological / physiological process.
- Cell and tissue organisation must obey classical mechanics. As these laws are very strict and unambiguous, they will put additional constraints on a biological system, therefore limiting the solution space.
- The inclusion of mechanical variables creates additional opportunities for model validation, as simulated and measured mechanical 'performance' must correspond.

In these mechanochemical models, mechanics was considered at the tissue scale and involved the definition of balance and constitutive laws at that scale (see also Ambrosi et al. (2011) for an excellent overview of the continuum mechanical treatment of biological growth and remodeling at the tissue scale). While these models have increased our understanding on the role of mechanics for tissue organization and e.g. pattern formation, we need models at the cell or even molecular scale if one wants to address the current challenges in mechanobiology- the field that studies how mechanical conditions regulate biological processes – and which are related to the understanding of mechanotransduction. Again, we can be inspired by Murray's motivation why and how we can incorporate mechanical principles in models that deal with cell behaviour. As classical mechanics is valid at cell and molecular length scales, we should explicitly impose it at the relevant length scales (such as e.g. a Langevin equation for describing the dynamics of molecular systems), in this way effectively restricting model solutions and therefore cell behaviour (motion) to those that respect these fundamental laws. Today we are witnessing such modelling efforts for the study of cell motility, like in the work of Kim and co-workers, who model a (3D) single cell as a collection of nodes (particles) on the cell and nuclear membrane. The nodal positions in time are obtained by defining (and solving) proper equations of motion that take into account cell mechanical forces acting upon the nodes, such as frictional forces, (membrane) elastic energy forces, focal adhesion forces (and their dynamics due to binding kinetics), stress fiber forces and lamellipodium forces (Kim et al., 2013).

Dealing with mechanics at cellular and subcellular (molecular) length scales is challenging (see e.g. Jacobs et al. (2012) for an excellent introduction to the subject). When formulating equations of motion, one needs to consider the kind of mechanical interactions (sources of mechanical forces) that are present and the appropriate constitutive laws at these length scales, which requires a profound understanding of (bio)polymer mechanics and which foundations are laid down in statistical mechanics. Clearly, cell and molecular mechanical modelling advances can only be made if the experimental tools to measure mechanical behaviour at these length scales are available. Today we have at our disposal a variety of advanced techniques that allow us to do so, such as atomic force microscopy, optical tweezers, magnetic twisting cytometry and traction force microscopy – but computational models are required to interpret the mechanical data, meaning that advances in experimental and computational cell mechanics have to go hand in hand!

The development of computational models that address mechanotransduction (mechano-chemical feedback) is even more challenging than trying to capture 'passive' cell mechanical behaviour. Not only should these models obey classical mechanics –at a time and length scale that is relevant for the processes at study – they need to capture the mutual interactions and dynamics that is implied by this feedback. The exact nature of such models is likely to be application-dependent, but they will be characterized by some 'multiphysics' and multiscale aspects, as on the one hand mechanical information (such as calculated by means of continuum-type or particle-based methods) needs to be coupled to chemical information (requiring e.g. models dealing with reaction kinetics or thermodynamics), while one the other hand molecular scales need to be coupled to cellular scales, which are often communicating with tissue and organ-level scales. Multiscale models coupling several of these aspects have already been developed e.g. for the study of cell motility, like Marée et al. (2012) who integrated a reaction-diffusion model of phosphoinositide and Rho family GTPase signaling into a (2D) Cellular Potts modelling framework to study the feedback from these molecular signals and cell shape on single cell polarization and motility. However in order to be able to validate them in terms of their mechanical performance (e.g. generation of tractional forces, which can be measured by means of traction force microscopy) such models should be extended with a more explicit treatment of classical mechanics. Finally, for generating hypotheses on mechano-chemical feedback computational and experimental efforts again must join forces: apart from the techniques mentioned previously to probe cell and molecular mechanical behaviour, fluorescence microscopy based techniques, such as Förster Resonance Energy Transfer (FRET) allow to monitor in a non-destructive way mechanics-induced conformational changes of sensor molecules, which not only can inform us on (mechanics-induced) molecular activation (Wang et al., 2005), but also on the molecular forces that are needed to do so (Wang et al., 2011).

Conclusion

There is a large body of (experimental) evidence that mechanical feedback is crucial for biological systems. Computational models that obey classical mechanics offer a number of advantages, as was already explored decades ago in the context of morphogenesis. We can be inspired by these seminal works to develop novel (multiscale) models that obey the same laws at cellular and subcellular scales, in order to study the mechanisms of mechano-chemical feedback. Combining computational and experimental approaches will be key to the advancement of mechanobiology.

References

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